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Rh(II)/Pd(0) Dual-Catalyzed Regio-Divergent Three-Component Propargylic Substitution

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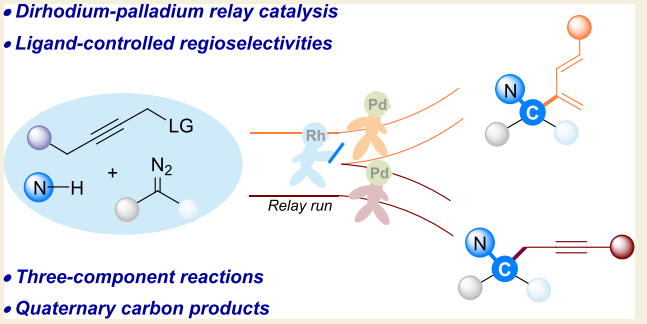
ABSTRACT: Regio-divergent propargylic substitution to generate functionally diverse products from identical starting materials remains a formidable challenge, probably due to the unpredictable regiochemical complexity. In practically, the synthesis of α-quaternary propargylic-substituted products is still much less developed, and preprepared nucleophiles are generally applied in this type of reaction with propargylic substrates, which limits the reaction efficiency and diversity of the obtained products. Herein, we disclose unprecedented three-component propargylic substitution of α-diazo esters with amines and propargylic carbonates under dirhodium/palladium dual catalysis. The key to the success of this multicomponent propargylic substitution is to avoid two-component side reactions through a tandem process of dirhodium(II)-catalyzed carbene insertion and palladium-catalyzed regiodivergent propargylic substitution. The judicious selection of a diphosphine (dppf) or monophosphine (ᵗBuBrettphos) as the ligand is crucial for the reaction to generate different products in a switchable way, α-quaternary 1,3-dienyl or propargylated products, with high regio- and chemoselectivities.



KEYWORDS: *dual catalysis, geminal-difunctionalization, regiodivergent propargylic substitution, diazo compounds, tandem catalysis*

1. INTRODUCTION

Transition-metal-catalyzed nucleophilic substitution reaction of propargyl electrophiles has emerged as an attractive method to form functionally diverse products,[1−8] such as 1,3-dienyl,[9−11] propargylated,[12−18] allenyl,[19−24] or double-addition products (Scheme 1a).[25−29] Despite the great advances in this area, previously developed propargylic substitutions were often confined to traditional two-component reactions using preprepared nucleophiles, which limited the diversity of the products and the reaction efficiency. In addition, the construction of α-quaternary substituted products using tertiary carbon nucleophiles is still much less developed[11,30−33] remains a formidable challenge, probably due to the large steric hindrance of the formed quaternary carbon center (Scheme 1b, left). Undoubtedly, both α-quaternary 1,3-dienes[34−39] and propargylic structural units[40−47] can play crucial roles in organic synthesis by offering handles for further synthetic transformations, especially for quick access to a variety of molecules with quaternary carbon centers. Therefore, it is highly desirable to develop a synthetic protocol for regio-divergent propargylic substitution to access these two types of α-quaternary substituted products in a controllable way, preferably from the assembling of multi-readily accessible reagents (Scheme 1b, right). However, using controlled reaction parameters to fine-tune the regioselectivity and chemoselectivity in such a reaction,[31,48−52] especially for multicomponent reactions, remains a formidable challenge, due to multiple reaction pathways of several possible coexisting intermediates and competitive two-component reactions.

Multicomponent reactions (MCRs) offer substantial advantages over traditional approaches for the expeditious construction of complex molecules in an atom- and step-economical manner.[53−55] Especially, the catalytic metal carbene *gem*-difunctionalization processes of nucleophiles, diazo compounds, and electrophiles, involving electrophilic interception of metal-associated ylide pioneered by Hu et al., have been demonstrated to be an effective strategy to construct complex molecular architectures with quaternary centers (Scheme 1c).[56−58] In addition, cross-coupling reactions of two reactants with a carbene moiety under transition metal catalysis have also proved to be highly efficient for the difunctionalization of diazo compounds.[59−61] Due to the great significance of the allylic group in organic synthesis, the combination of carbene difunctionalization with allylation has attracted great attention. Two-component reactions of diazo

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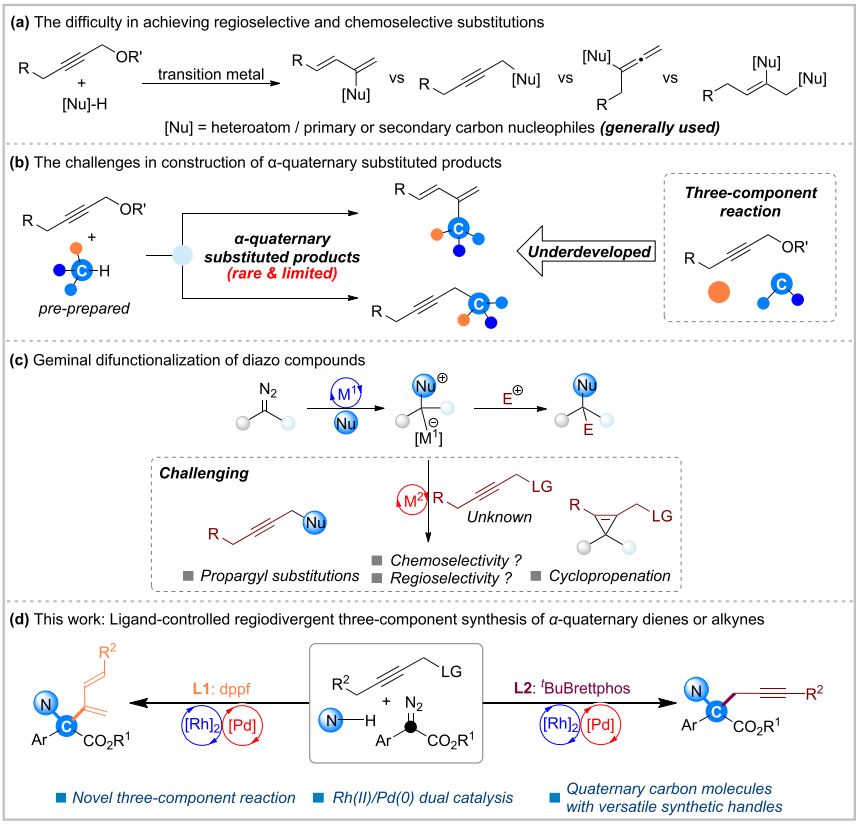
Scheme 1. Regio-Divergent Three-Component Propargylic Substitution



compounds enabled by bimetallic dual catalysis have been developed by the generation of a nucleophile in situ from an intramolecular carbene insertion followed by allylic substitution.[62−65] Recently, our group developed a novel Rh(II)/xantphos catalyzed three-component reaction of nucleophiles, diazo compounds, and allylic electrophiles, leading to the formation of α-quaternary allylic products.[66−71] Hu and co-workers reported a three-component asymmetric allylation of α-diazo carbonyl compounds with alcohols and allyl carbonates, by employing a ternary cooperative catalysis of an achiral Pd-complex, $Rh_2(OAc)_4$, and a chiral phosphoric acid.[72] Huang and co-workers reported a palladium-catalyzed three-component allylation of α-diazo carbonyl compounds with anilines and allyl carbonates.[73] However, compared with allylation, so far there are no documented examples on the use of nucleophiles and propargylic electrophiles in three-component reactions of diazo compounds.[74] The potential challenges in developing such a protocol are (1) the greater complexity in achieving regioselective and chemoselective propargylic substitution than that of allylic substitution owing to the product diversity;[1−8] (2) the competitive direct propargylic substitutions between the nucleophilic substrates and propargylic substrates; and (3) possible side reaction such as dirhodium(II)-catalyzed cyclopropenation reaction between diazo compounds and triple bond of propargylic substrates.[75]

The combined use of two or even more metal catalysts to construct new C−C and C−X bonds in a single operation has attracted widespread attention since novel reactivity and selectivity might be achieved together with a bonus of simplified workup procedures.[76−82] In particular, bimetallic and tandem catalysis has emerged as an efficient and reliable method to enable a series of new transformations,[83−90] which might offer potential opportunities to achieve the difunctionalization of diazo compounds together with propargylation in MCRs. Herein, we report a dirhodium(II)/palladium(0) dual-catalyzed ligand-controlled regio-divergent three-component propargylic substitution, which uses an α-diazo ester and an amine to generate a nucleophilic intermediate in situ, followed by a regio-divergent propargylic substitution via Pd catalysis (Scheme 1d). Notably, the regio- and chemoselectivities can be fine-tuned via ligand modulation, affording efficient synthesis of either α-quaternary 1,3-dienyl or propargylated products, respectively, that are otherwise difficult to access.

2. RESULTS AND DISCUSSION

2.1. Reaction Optimization

We initiated our studies by employing *N*-methylaniline **1a**, α-diazo ester **2a**, and propargylic carbonate **3a** as the model substrates, and the reaction was carried out in the presence of $Rh_2(Oct)_4$ (1.0 mol %), $Pd_2(dba)_3$ (3.0 mol %), dppf (8.0 mol %), and Cs_2CO_3 in MeCN at 80 °C. To our delight, the desired products **4a** and **5a** were obtained, albeit both in less satisfactory yields, respectively (entry 1, Table 1). Under otherwise identical conditions, changing the Pd precursor to $Pd(PPh_3)_4$, $[Pd(allyl)Cl]_2$ and $Pd(OAc)_2$ failed to afford better results than those observed with $Pd_2(dba)_3$ (entries 2−4). In addition, modification of the anions of Rh(II) carboxylate led to no enhancement in the reaction efficiency (entries 5−6). Further attempts to improve the catalytic efficiency were made by surveying a variety of phosphine ligands in the reaction (entries 7−10). Notably, dppf gave the best result to access 1,3-diene **4a** in 47% yield along with **5a** in 22% yield (entry 1), while the sterically bulky monophosphine ligand, ^{t}BuBrett-

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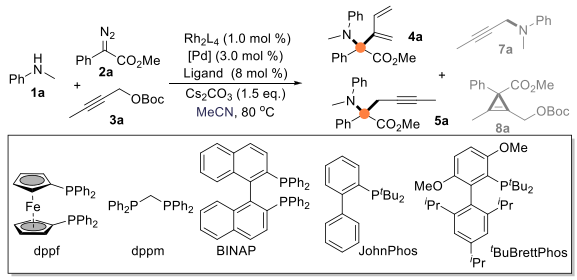
Table 1. Optimization of the Reaction Conditions[a]



Entry	Rh_2L_4	[Pd]	Ligand	**4a** (%)[b]	**5a** (%)[b]
1	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	dppf	47	22
2	$Rh_2(Oct)_4$	$Pd(PPh_3)_4$	-	8	16
3	$Rh_2(Oct)_4$	$[Pd(allyl)Cl]_2$	dppf	47	40
4	$Rh_2(Oct)_4$	$Pd(OAc)_2$	dppf	22	13
5	$Rh_2(OAc)_4$	$Pd_2(dba)_3$	dppf	6	3
6	$Rh_2(esp)_4$	$Pd_2(dba)_3$	dppf	29	8
7	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	dppm	0	0
8	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	BINAP	47	37
9	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	JohnPhos	0	45
10	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	^{t}BuBrettPhos	0	75
11[c]	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	dppf	55	21
12[c,d]	**$Rh_2(Oct)_4$**	**$Pd_2(dba)_3$**	**dppf**	**80**	**16**
13[c,e]	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	dppf	32	13
14[f]	$Rh_2(Oct)_4$	$Pd_2(dba)_3$	^{t}BuBrettPhos	0	85
15[f,g]	**$Rh_2(Oct)_4$**	**$Pd_2(dba)_3$**	**^{t}BuBrettPhos**	**0**	**96**
16	$Rh_2(Oct)_4$	-	dppf	0	0
17	-	$Pd_2(dba)_3$	dppf	9	10

[a]Unless otherwise noted, the reaction conditions are as follows: **1a** (0.2 mmol), **2a** (0.24 mmol), **3a** (0.22 mmol), MeCN (2 mL), Rh_2L_4 (1.0 mol %), [Pd] (3.0 mol %), ligand (8.0 mol %), Cs_2CO_3 (1.5 equiv), 80 °C, 12.0 h, N_2. [b]Yield was determined by ^{1}H NMR. [c]$Rh_2(Oct)_4$ (2.0 mol %). [d]60 °C. [e]50 °C. [f]Cs_2CO_3 (3.0 equiv). [g]**1a** (1.0 equiv), **2a** (1.1 equiv), **3a** (1.5 equiv).

Phos, demonstrated optimal selectivity for propargylated product **5a** (75%, entry 10). The yield of **4a** was improved to 55% when the amount of $Rh_2(Oct)_4$ was increased to 2 mol % (entry 11). Further improvement in the yield of **4a** was observed when the temperature was lowered to 60 °C (**4a**, 80%; **5a**, 16%; entry 12). On the other hand, the yield of **5a** was improved to 85% when the amount of Cs_2CO_3 was increased to 3.0 equiv (entry 14), and it was further improved to 96% when the reaction was carried out with **1a** (1.0 equiv), **2a** (1.1 equiv), and **3a** (1.5 equiv) (entry 15). In addition, controlled experiments showed that without the Pd catalyst, the reaction did not proceed, and no **4a** or **5a** was detected (entry 16). In the absence of the dirhodium catalyst, only a trace amount of desired products **4a** and **5a** was observed (entry 17). It should be noted that none of the possible direct propargylamination product **7a** or cyclopropenation product **8a** was observed in all of the cases.

2.2. Scope of 1,3-Dienylation

With the optimal conditions in hand, we next investigated the generality of the reaction substrates under conditions A (entry 12 in Table 1), with a preference for the synthesis of products bearing a 1,3-dienyl motif (Scheme 2a). We were delighted to find that diverse *N*-alkylanilines reacted smoothly with substrates **2a** and **3a** under the standard conditions, affording the desired products **4a**−**4c** in moderate to good yields (40−75%). Besides, *N*-benzylaniline **1d**, *N*-allylaniline **1e**, and 3-(phenylamino)propanenitrile **1f** were also well tolerated in the reactions, giving the corresponding products **4d**−**4f** in moderate yields (40−55%). Anilines with either electron-donating (**1g**, **1i**−**1j**) or electron-withdrawing substituent(s) (**1h**, **1k**−**1m**) on the *meta*- or *para*-position of the phenyl ring were compatible with the procedure, providing the corresponding products **4g**−**4m** in 47−74% yields. To our delight, indoline **1n** and 1,2,3,4-tetrahydroquinoline **1o** were also found as competent substrates in the reaction, affording the multisubstituted products **4n** and **4o** in 50 and 58% yields, respectively. Additionally, the reactions of substituted indoline and 1,2,3,4-tetrahydroquinoline also proceeded smoothly, giving the corresponding products **4p**−**4r**, respectively, in good yields. However, aniline, primary alkyl amine, and dialkyl amine were not suitable substrates under reaction conditions A.

We also examined the substrate scope with respect to the α-diazo esters **2** in the reactions with *N*-methylaniline (**1a**) and propargylic carbonate **3a**. As shown in Scheme 2b, diazo esters with either electron-withdrawing (F−, Cl−) or electron-donating (Me−, ^{t}Bu−, MeO−, BnO−) groups on the aryl group performed well in the reaction, providing the corresponding products **4s**−**4aa** in moderate to good yields (42−75%). Moreover, the structure of **4aa** was unambiguously determined by X-ray crystallographic analysis (see the SI). In addition, 3,4-dichloro substituted phenyl **2ab** also reacted smoothly in the reaction, giving the corresponding product **4ab** in 58% yield. The 2-naphthyl (**2ac**) and 3-thienyl (**2ad**) motif (**2ad**) in diazo reactants were also tolerated well in the reaction, affording the products **4ac** and **4ad** in 75 and 50% yields, respectively. Changing the methyl ester of the diazo compound to ethyl (**2ae**), benzyl (**2af**), benzhydryl (**2ag**), 2-methylbenzyl (**2ah**), 1-naphthyl (**2ai**), or 2-naphthyl ester (**2aj**), the reactions still proceeded well, giving the corresponding products in 62−73% yields (**4ae**−**4aj**).

With the functional group tolerance of the reaction having been evaluated for *N*-alkylanilines **1** and α-diazo esters **2**, some propargylic carbonates were investigated (Scheme 2c). All of the tested propargylic alcohol esters **3b**−**3d** reacted well in the reaction, affording product **4a** in good yields (60−70%). However, a terminally substituted ethyl or butyl propargylic carbonate resulted in significantly decreased yields (**4ak** and **4al**) as compared to the reaction of model substrate **3a**. On the other hand, the reaction involving terminal cyclopropyl, allyl substituents, or propargylic carbonate with internal alkyl substituents failed to generate the target products (**4am**−**4ao**), probably caused by severe steric hindrance.

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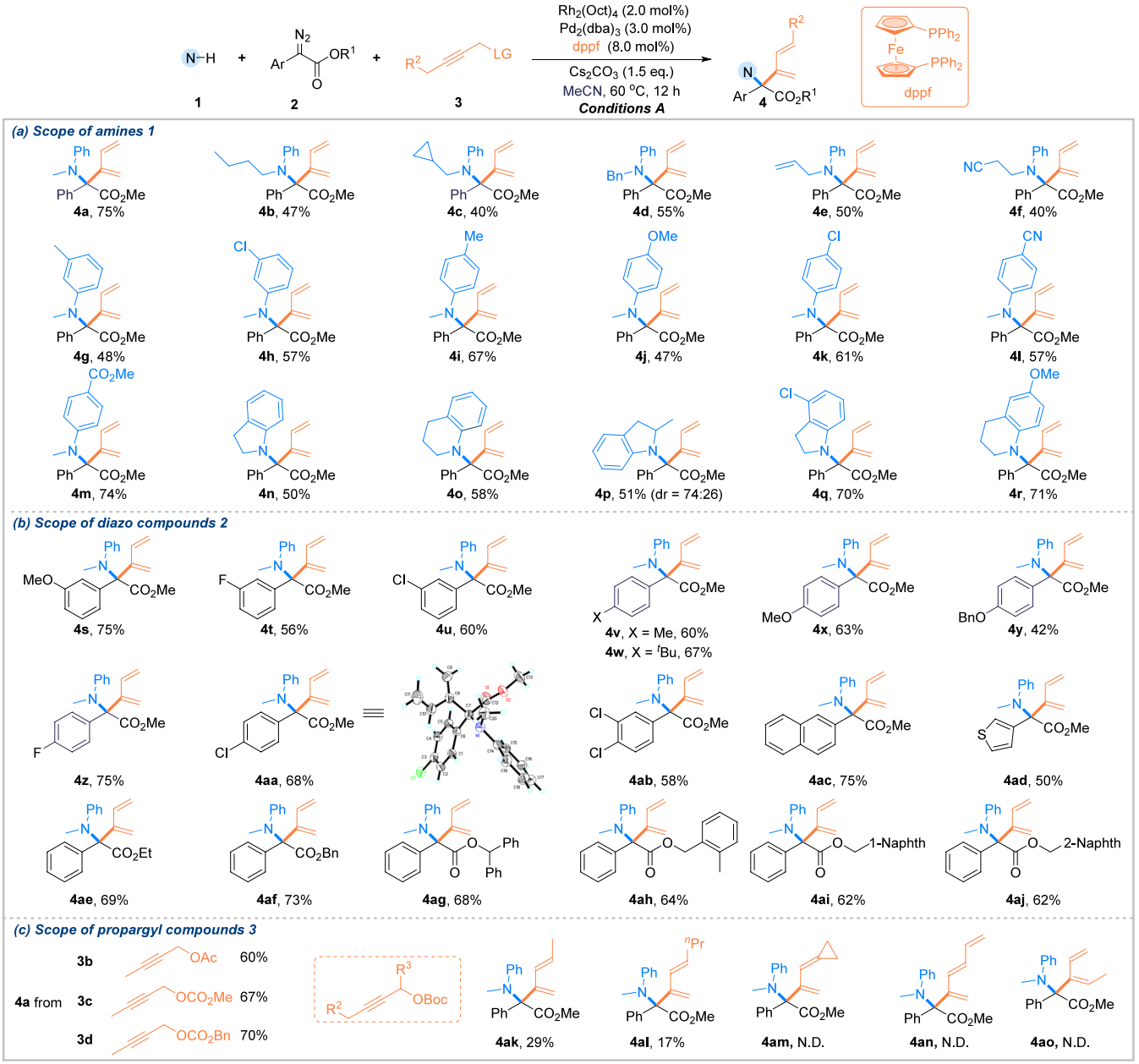
Scheme 2. Scope of 1,3-Dienylation[a]



[a]Reaction conditions A: **1** (0.2 mmol, 1.0 equiv), **2** (0.24 mmol, 1.2 equiv), **3** (0.22 mmol, 1.1 equiv), MeCN (2.0 mL), $Rh_2(Oct)_4$ (2.0 mol %), $Pd_2(dba)_3$ (3.0 mol %), dppf (8.0 mol %), Cs_2CO_3 (1.5 equiv), 60 °C, 12.0 h. Isolated yields.

2.3. Scope of Propargylation

With the 1,3-dienylation of various reaction substrates having been examined, we further surveyed the substrate scope for propargylation under conditions B (entry 15 in Table 1), in an effort to evaluate the applicability of this ligand-controlled regiodivergent reaction. Analogous to the results of the 1,3-diene synthesis discussed above, a broad range of *N*-alkylanilines underwent the transformation smoothly, giving the desired propargylated products **5a**−**5r** in good to excellent yields (50−99%, Scheme 3a). Notably, it was found that the prototype aniline was also well tolerated in the reaction, providing the corresponding product **5s** in a 53% yield. However, primary alkyl amine or dialkyl amine was found to be not tolerated under reaction conditions B. The reactions involving various substituted *α*-diazo esters also proceeded well, affording the corresponding products **5t**−**5ak** in moderate to high yields (66−98%, Scheme 3b). The structure of **5ab** was confirmed by X-ray crystallographic analysis (see the SI). The reactions of propargylic carbonates **3b**−**3d** with different leaving groups also provided good results (74−80%). To our delight, in contrast to their poor reactivity for dienylation, terminally substituted ethyl, butyl, and cyclopropyl propargylic carbonates were tolerated well in the propargylation and resulted in the production of products **5al**−**5an** in high yields (89−97%, Scheme 3c). However, both terminal allyl substituents along with internal alkyl substituents on the propargylic carbonate hindered the product formation.

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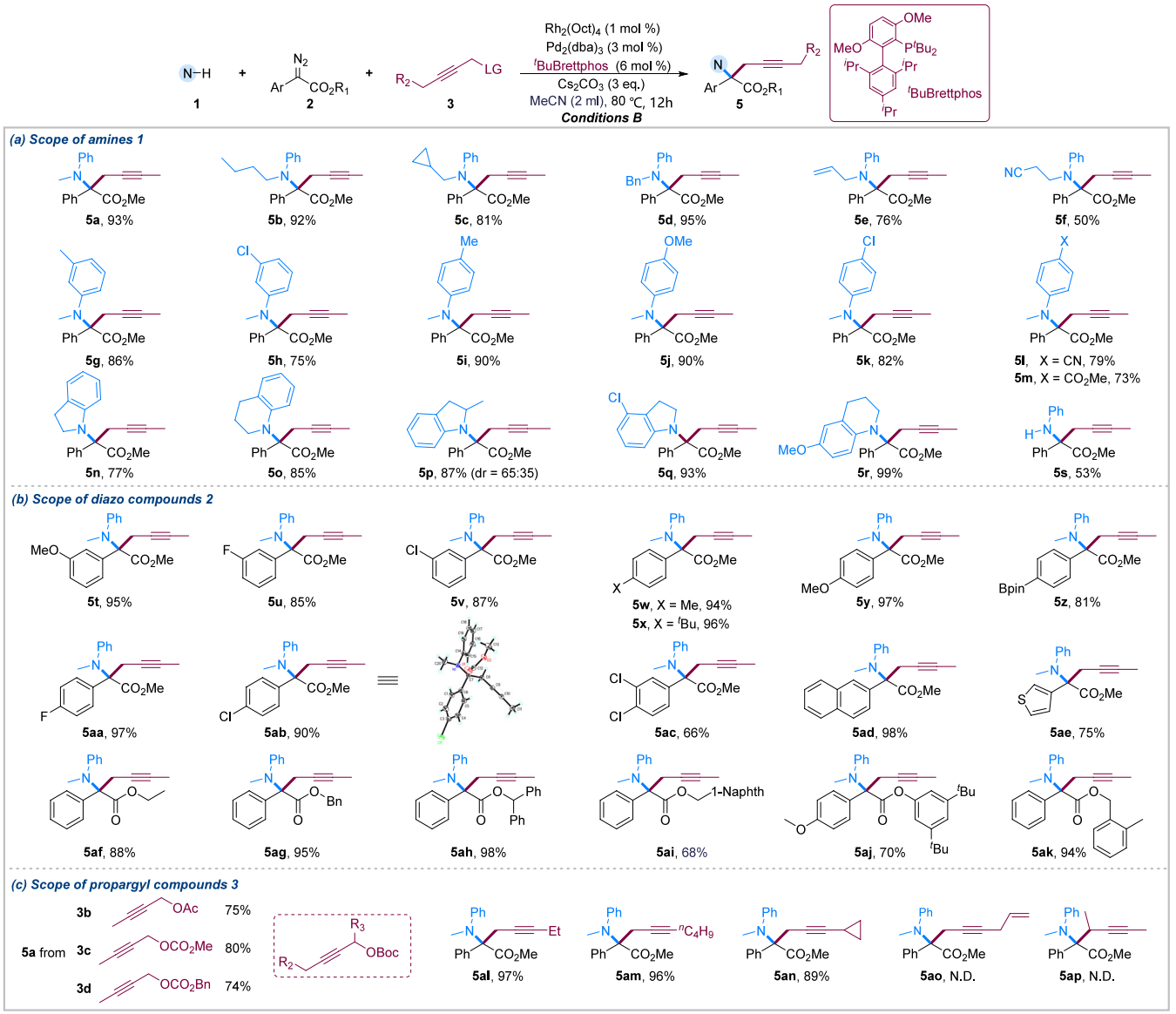
Scheme 3. Scope of Propargylation[a]



[a]Reaction conditions B: **1** (0.2 mmol, 1.0 equiv), **2** (0.22 mmol, 1.1 equiv), **3** (0.3 mmol, 1.5 equiv), MeCN (2.0 mL), $Rh_2(Oct)_4$ (1.0 mol %), $Pd_2(dba)_3$ (3.0 mol %), ^{t}BuBrettPhos (6.0 mol %), Cs_2CO_3 (3.0 equiv), 80 °C, 12.0 h. Isolated yields.

2.4. Synthetic Applications

To show the applicability of these approaches, we next set out to perform late-stage modification of complex architectures derived from various biologically active natural products and drug molecules (Scheme 4a), such as α-diazo ester derived from isoxepac (**9a**, **10a**), (*S*)-(−)-β-citronellol (**9b**, **10b**), (−)-nopol (**9c**, **10c**), diacetone-*D*-galactose (**9d**, **10d**), dehydroepiandrosterone (**9e**, **10e**), and *D*-menthol (**10f**). To our delight, moderate to excellent yields were achieved in both 1,3-dienylation (**9a**−**e**, 56−90%) and propargylation (**10a**−**f**, 79−99%), showing the great potential of these approaches for drug design. Furthermore, under either standard conditions A or B, gram-scale reactions of **1a**, **2a**, and **3a** proceeded smoothly to afford the desired products **4a** (1.30 g, 71%) and **5a** (1.45 g, 94%), respectively (Scheme 4b). Considering the 1,3-diene unit as a versatile synthetic handle, product **4a** was used for diversified transformations. In the presence of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione, **4a** underwent the Diels−Alder reaction smoothly, followed by *N*-methyl aniline unit migration and cyclization to produce **11a** in 60% yield. Notably, the structure of **11a** (major isomer) was confirmed by X-ray crystallographic analysis (see the SI). In addition, Diels−Alder reactions between **4a** and other dienophiles, such as dimethyl but-2-ynedioate (DMAD), 1-methyl-1*H*-pyrrole-2,5-dione, and 1,2-dibromobenzene also proceeded well, affording the corresponding products in 64−96% yields (**11b**−**11d**). Furthermore, iridium-catalyzed hydroboration of **4a** with HBPin led to organoboron **11e** in 56% yield, which can serve as a versatile building block for further derivatizations. Moreover, the ester group of **4a** can be reduced by DIBAL-H to obtain alcohol **11f** in 73% yield. Finally, treatment of **4a** at 70 °C in the presence of trifluoromethanesulfonic acid afforded the product **11g** in 41% yield via *ortho* Claisen rearrangement followed by a lactonization. Furthermore, selected transformations of propargylated product **5a** were also examined. The ester group of **5a** could be reduced to alcohol **12a** with

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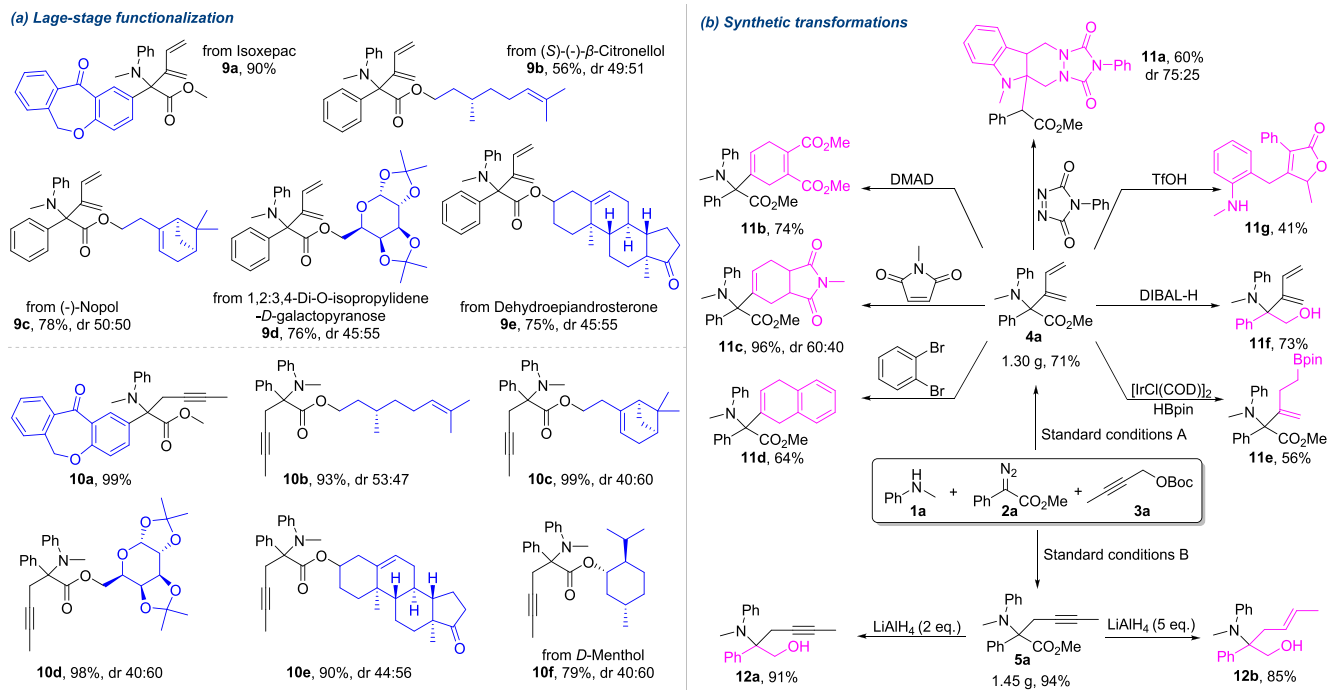
Scheme 4. Late-Stage Functionalization of Complex Architectures and Synthetic Transformations



$LiAlH_4$, and the carton−carton triple bond could be selectively reduced to a double bond by increasing the amount of $LiAlH_4$ to produce **12b** in 85% yield.

2.5. Mechanistic Studies

To gain some mechanistic insights into the regiodivergent MCRs, several experiments were conducted, and the results are shown in Scheme 5. The kinetic profiles for the reaction of **1a**, **2a**, and **3a** under the standard conditions A clearly showed that compound **6a** was generated rapidly in the first 5 min and was further transformed into final product **4a**. These results suggested that the catalysis most likely runs via a tandem process, with **6a** possibly acting as a nucleophile generated in situ from the reaction of **1a** and **2a** and was consumed in the subsequent reaction with **3a**. A series of control experiments verified the necessity of each reaction component (Scheme 5A,a). The reaction failed to give any traces of either **4a** or **6a** in the absence of $Rh_2(Oct)_4$, probably due to the suppression of the carbene insertion reaction. Without $Pd_2(dba)_3$ or dppf, a significant amount of **6a** was observed (43 and 87%, respectively) without detection of **4a**, suggesting that $Pd_2(dba)_3$ and dppf should be responsible for the propargylic substitution. In addition, in the absence of Cs_2CO_3, the reaction resulted in a significantly decreased yield of **4a** (34%), indicating that a base-assisted deprotonation process is beneficial for propargylic substitution. Then, we carried out the deuterium labeling studies to gain more insight into the reaction mechanism. As shown in Scheme 5A,b−d, the deuterated methyl 2-(methyl(phenyl)amino)-2-phenylacetate **6a−D** was used to react with propargylic carbonate **3a,** resulting in a H/D ratio of 88:12 at the internal carbon of the diene (Scheme 5A,b). Next, terminally deuterated propargylic carbonate **3a−D** was used in the reaction with **1a** and **2a**, also producing the product with an 88:12 H/D ratio at the internal carbon (Scheme 5A,c). These results demonstrate that together with benzylic H on **6a**, N−H of **1a**, the terminal methyl group of **3a** also acts as a proton source of the diene, probably due to a base-mediated H-elimination of the Me group of **3a** during the catalysis. In addition, the reactions using **3a−D** and CD_2-substituted propargylic carbonate **3a−D′** gave the 1,3-dienylation products **4a−D″** and **4a−D‴**, respectively, with the maintenance of "D" on C4 or C1, suggesting that the in-situ-generated nucleophile always attacks the C2 site of the propargylic carbonate.

Analogous to the results of 1,3-dienylation, the kinetic profile for the propargylation reaction of **1a**, **2a**, and **3a** under standard conditions B indicated that compound **6a** was formed within 5 min, which was then further transformed to the final product **5a**. These results also showed a tandem process is most likely to be involved in the catalysis. The control experiments revealed that in the absence of either $Rh_2(Oct)_4$ or Cs_2CO_3, only a moderate or trace amount of the desired propargylated product **5a** was observed. Moreover, no product was formed in the absence of $Pd_2(dba)_3$ or the phosphine ligand ^{t}BuBrettPhos (Scheme 5B,a). Similar deuterium labeling experiments on the propargylation were carried out (Scheme 5B,b−d). Using deuterated **6a−D**, no deuterium substitution product was generated, indicating that there is no protonation process in the reaction. Additionally, when deuterated propargyl carbonates **3a−D** and **3a−D′** were employed in the reactions with **1a** and **2a**, the corresponding CD_3 and CD_2 remained at C1 and C4, respectively. These results indicated that the nucleophilic attack occurred preferentially on the α-carbon position of the leaving group to produce the final propargylated product.

Finally, to verify the possible involvement of a tandem process in both 1,3-dienylation and propargylation reactions, we carried out stepwise reactions of *N*-methyl aniline (**1a**), α-diazo ester **2a,** and propargylic carbonate **3a** (Scheme 5C). First, only using Rh(II) carboxylate as the catalyst made **1a** react with α-diazo ester **2a** to generate the carbene insertion product **6a** in 86% yield. Next, when isolated product **6a** was treated with propargylic carbonate **3a** by using $Pd_2(dba)_3$/dppf or $Pd_2(dba)_3$/^{t}BuBrettPhos in MeCN, corresponding products

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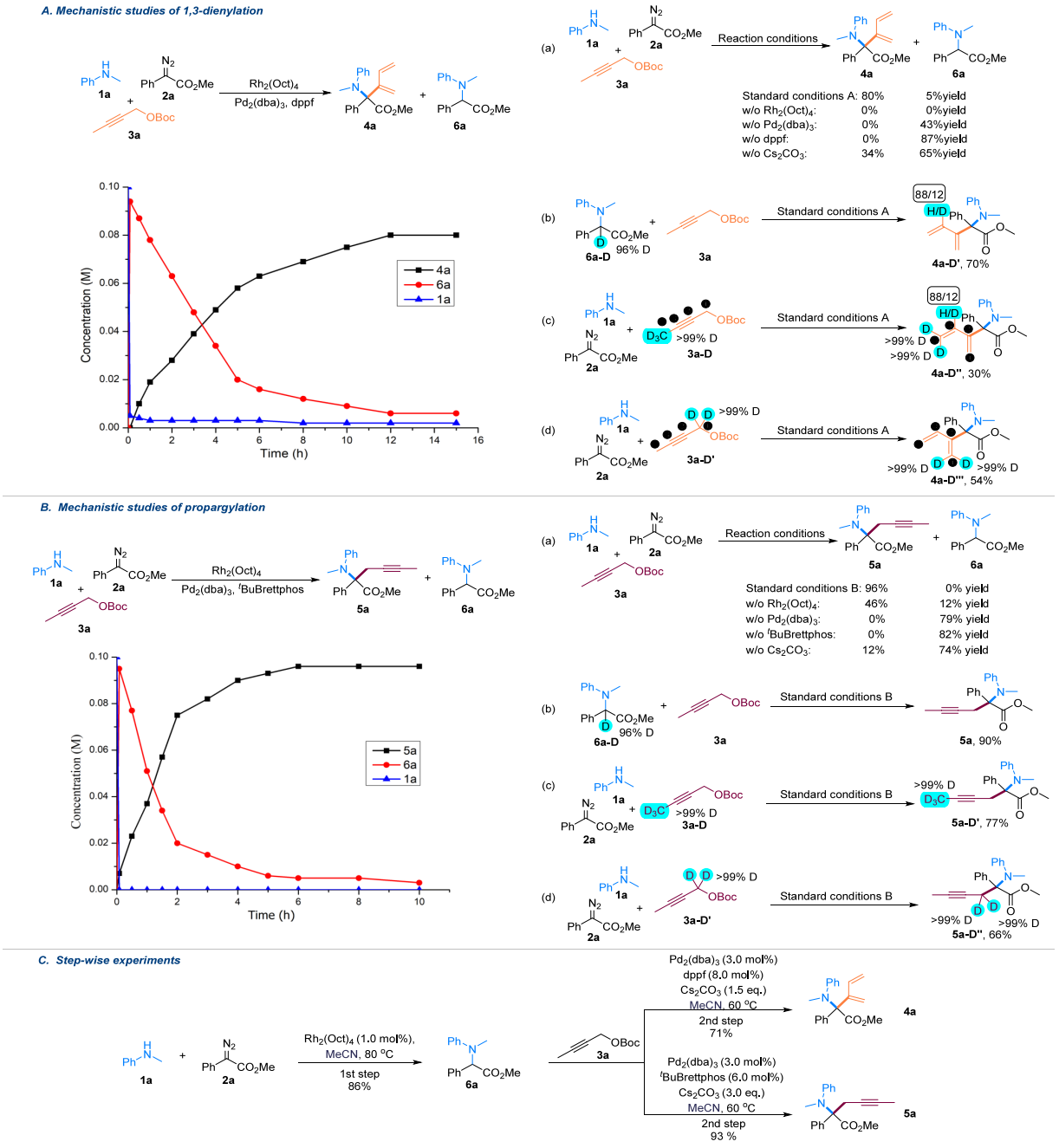
Scheme 5. Mechanistic Studies[a]



[a](A) Mechanistic studies of 1,3-dienylation. Reaction profiles of the MCR (Left), controlled experiments (Right, a), and deuterium labeling experiments (Right, b–d). (B) Mechanistic studies of propargylation. Reaction profiles of the MCR (Left), controlled experiments (Right, a), and deuterium labeling experiments (Right, b–d). (C) Stepwise experiments.

4a and **5a** were formed in 71 and 93% yields, respectively. These results clearly revealed that this ligand-controlled regiodivergent reaction is a relay Rh(II)/Pd(0) dual catalysis and the reaction sequence in one pot could provide superior efficiency compared to the stepwise transformations.

Based on these results and the literature, a plausible mechanism for the relay Rh(II)/Pd(0) dual catalysis was proposed, as illustrated in Scheme 6. The Rh(II)-carbenoid **A** can be first generated in situ from the reaction of phenyl diazoacetate **2a** with phosphine-free [$Rh(II)_2$]. Then, **A** was trapped by *N*-methyl aniline (**1a**) to give ammonium ylide intermediate **B**, which was further converted to N–H insertion product **6a** through [1,2]-proton transfer. In the relay catalysis pathway, propargyl carbonate **3a** underwent an oxidative addition onto palladium(0), releasing CO_2 and a *tert*-butanol anion to form π-propargyl complex **C**.[91−93] In the presence of a base, the attack of **6a** to the central carbon of π-propargyl moiety would form a pallada-cyclobutene intermediate **E**.[94] Subsequent protonation of the sp^2 carbon–palladium bond with *tert*-butyl alcohol would give π-allyl palladium intermediate **F**. Finally, base-induced deprotonation of the terminal methyl proton can yield 1,3-diene **4a** and regenerate the palladium(0) catalyst (Scheme 6, path a). On the other hand, it is well-known that η^3-(propargyl)palladium complex **C** can

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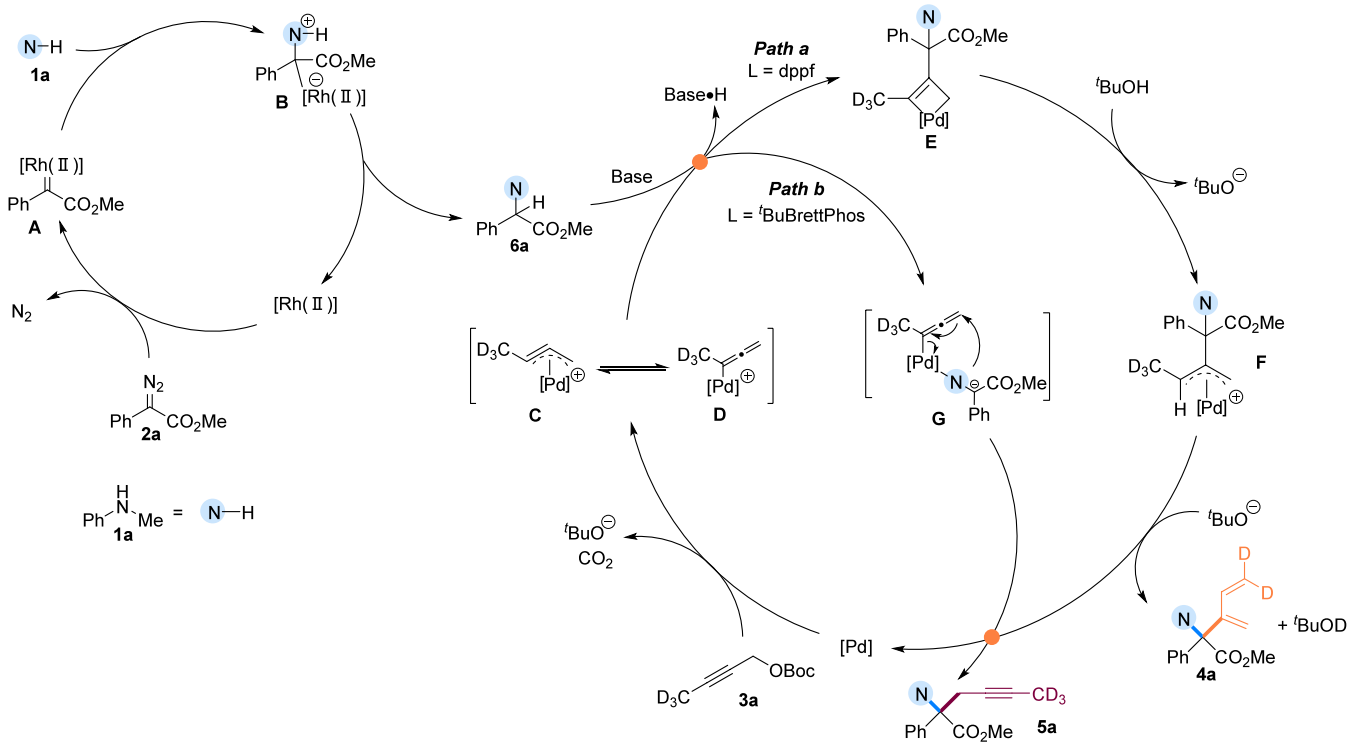
Scheme 6. Possible Reaction Pathway



undergo isomerization to η^1-(allenyl)palladium species **D**.[91,92] It is possible for **6a** to coordinate with [Pd] to form an intermediate **G**, followed by an inner-sphere nucleophilic attack at the terminal allenyl carbon to provide the final propargylated product **5a** (Scheme 6, path b).[17] As an alternative, the direct attack of **6a** on the terminal carbon of the η^1- or η^3-(propargyl)palladium complexes can also generate propargylated product **5a**. The selectivities between the competing 1,3-dienylation and propargylation pathways are elusive, which might be proposed to be switched by the denticity of the phosphine ligands.[31]

3. SUMMARY AND CONCLUSIONS

In conclusion, a dirhodium(II)/palladium(0) dual catalyzed ligand-controlled regiodivergent three-component propargylic substitution reaction of amines, diazo compounds, and propargylic carbonates has been developed, wherein the use of palladium-dppf allowed the synthesis of 1,3-dienes, while the employment of palladium-^{t}BuBrettPhos allowed the synthesis of propargylated products. Mechanistic studies suggest that the reaction is likely to proceed via a tandem process of carbene-induced N−H functionalization and sequential Pd(0)-catalyzed regiodivergent propargylic substitution. We expect that this ligand-controlled regiodivergent strategy will create possibilities for novel reaction emergence and encourage broad application to diversity-oriented synthesis in the future.

4. METHODS

4.1. Typical Experimental Procedure for the Three-Component Reaction of 1,3-Dienylation

In an oven-dried 10 mL sealed tube equipped with a stir bar was added $Rh_2(Oct)_4$ (3.2 mg, 4×10^{-3} mmol, 2.0 mol %), $Pd_2(dba)_3$ (5.5 mg, 6×10^{-3} mmol, 3.0 mol %), dppf (8.9 mg, 1.6×10^{-2} mmol, 8.0 mol %), and Cs_2CO_3 (97.7 mg, 0.3 mmol, 1.5 equiv) under a dry argon atmosphere. Then, amine compound **1** (0.2 mmol, 1.0 equiv), propargylic carbonate **3** (0.22 mmol, 1.1 equiv), anhydrous CH_3CN (2.0 mL), and diazo compound **2** (0.24 mmol, 1.2 equiv) were introduced using a syringe sequentially. The resulting mixture was stirred at 60 °C for 12.0 h. Then, the mixture was filtered, and a clear filtrate was collected. After removing the solvents in vacuo, the crude product was purified by flash column chromatography on basic aluminum oxide to give the desired product **4**.

4.2. Typical Experimental Procedure for the Three-Component Reaction of Propargylation

In an oven-dried 10 mL sealed tube equipped with a stir bar was added $Rh_2(Oct)_4$ (1.6 mg, 2×10^{-3} mmol, 1.0 mol %), $Pd_2(dba)_3$ (5.5 mg, 6×10^{-3} mmol, 3.0 mol %), ^{t}BuBrettPhos (5.8 mg, 1.2×10^{-2} mmol, 6.0 mol %), and Cs_2CO_3 (195.5 mg, 0.6 mmol, 3.0 equiv) under a dry argon atmosphere. Then, amine compound **1** (0.2 mmol, 1.0 equiv), propargylic carbonate **3** (0.3 mmol, 1.5 equiv), anhydrous CH_3CN (2.0 mL), and diazo compound **2** (0.22 mmol, 1.1 equiv) were introduced by syringe sequentially. The resulting mixture was stirred at 80 °C for 12.0 h. Then, the mixture was filtered, and the clear filtrate was collected. After the solvents were removed in vacuo, the crude product was purified by flash column chromatography on silica gel to give the desired product **5**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00415.

Experimental procedures; complete characterization data; and copies of ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR spectra (PDF)

Crystallographic data of **4aa** (CIF)

Crystallographic data of **5ab** (CIF)

Crystallographic data of **11a** (CIF)

CheckCIF data of **4aa** (PDF)

CheckCIF data of **5ab** (PDF)

CheckCIF data of **11a** (PDF)

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Notes

The authors declare no competing financial interest.

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